

## WHAT IS CLAIMED IS:

1. A variant of a heregulin, said variant having an amino acid sequence not found in nature and the ability to bind an ErbB receptor, wherein said variant comprises an amino acid substitution at a selected residue corresponding to a residue of 645-amino acid native human heregulin- $\beta$ 1 selected from the group consisting of:
- S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206, R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, S228, and F229.
- wherein said residues of 645-amino acid native human heregulin- $\beta$ 1 are numbered from the N-terminus of native human heregulin- $\beta$ 1, and wherein the amino acid substitution is not a replacement of the selected residue with an epidermal growth factor (EGF) residue corresponding to the selected residue.
2. The heregulin variant of Claim 1 wherein said selected residue is selected from the group consisting of:
- H178, L179, K187, N192, G193, G194, E195, R207, K211, T217, G218, Q222, and Y224.
3. The heregulin variant of Claim 1 wherein said heregulin is a human heregulin.
4. The variant of Claim 3 wherein said human heregulin is heregulin- $\beta$ 1.
5. The heregulin variant of Claim 1 wherein said heregulin variant is a fragment.

6. The heregulin variant of Claim 5 wherein said fragment comprises residues corresponding to a portion of human heregulin- $\beta$ 1 extending from about residue 175 to about residue 230.
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7. The heregulin variant of Claim 6 wherein said heregulin is a human heregulin.
8. The heregulin variant of Claim 7 wherein said human heregulin is human heregulin- $\beta$ 1.
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9. A variant of human heregulin- $\beta$ 1, said variant having an amino acid sequence not found in nature and the ability to bind an ErbB receptor, wherein said variant comprises an amino acid substitution selected from the group consisting of:
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- S177W; H178S, E, R, or A; V180Q, I, or E; K181P or A; A183G; E184V, W, K, R, G, or N; K185E, S, Q, or G; E186R; K187E or A; T188Q; E195Q; F197Y; M198R or K; K200R; D201T or I; P205T or Y; S206K, H, G, P, or R; R207Y; Y208R or L; L209M or G; K211R; P213S, T, N, or K; N214L, K, S, or E; F216M; N223H or W; and M226I
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- wherein residues of are numbered from the N-terminus of 645-amino acid native human heregulin- $\beta$ 1.
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10. The heregulin variant of Claim 9 wherein said heregulin variant comprises a set of amino acid substitutions selected from
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- A183G, E184W, K185D, E186R, K187E, T188G, M226I;
- A183D, E184K, K185S, E186R, K187E, T188G, M226I;
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- F197Y, M198K, K200R, D201I, M226I;
- P205Y, S206G, R207Y, Y208L, L209M;
- P205Y, S206R, R207Y, Y208R, L209M, M226I;

- P205T, S206H, R207Y, Y208R, L209M;  
 P205T, S206K, R207Y, Y208R, L209G;  
 N223W, M226I;  
 N223H, M226I;  
 5 S177W, H178E, K181P, A183G, E184W, K185D,  
 E186R, K187E, T188G, M226I;  
 P205Y, S206G, R207Y, Y208L, L209M, M226I;  
 A183G, K185E, E186R, K187E, T188G, F197Y,  
 M198R, D201T;  
 10 A183G, K185E, E186R, K187E, T188G, P205Y,  
 S206G, R207Y, Y208L, L209M;  
 A183G, K185E, E186R, K187E, T188G, F197Y,  
 M198R, D201T, P205Y, S206G, R207Y, Y208L, L209M;  
 A183G, K185E, E186R, K187E, T188G, M226I;  
 15 F197Y, M198R, D201T, P205Y, S206G, R207Y,  
 Y208L, L209M;  
 F197Y, M198R, D201T, P205Y, S206G, R207Y,  
 Y208L, L209M, M226I;  
 F197Y, M198R, D201T, M226I;  
 20 A183G, K185E, E186R, K187E, T188G, F197Y,  
 M198R, D201T, M226I;  
 A183G, K185E, E186R, K187E, T188G, P205Y,  
 S206G, R207Y, Y208L, L209M, M226I;  
 A183G, K185E, E186R, K187E, T188G, F197Y,  
 25 M198R, D201T, P205Y, S206G, R207Y, Y208L, L209M,  
 M226I;  
 F197Y, M198R, D201T, P205Y, S206G, R207Y,  
 Y208L, L209M, N223H, M226I; and  
 A183G, K185E, E186R, K187E, T188G, F197Y,  
 30 M198R, D201T, P205Y, S206G, R207Y, Y208L, L209M,  
 N223H, M226I.
11. The heregulin variant of Claim 10 wherein said  
 heregulin variant comprises a set of amino acid  
 35 substitutions selected from  
 A183G, E184W, K185D, E186R, K187E, T188G,  
 M226I;

- P205Y, S206G, R207Y, Y208L, L209M;  
N223H, M226I;  
P205Y, S206G, R207Y, Y208L, L209M, M226I;  
A183G, K185E, E186R, K187E, T188G, F197Y,  
5 M198R, D201T;  
A183G, K185E, E186R, K187E, T188G, M226I;  
F197Y, M198R, D201T, P205Y, S206G, R207Y,  
Y208L, L209M;  
F197Y, M198R, D201T, P205Y, S206G, R207Y,  
10 Y208L, L209M, M226I;  
F197Y, M198R, D201T, M226I;  
A183G, K185E, E186R, K187E, T188G, F197Y,  
M198R, D201T, M226I;  
A183G, K185E, E186R, K187E, T188G, P205Y,  
15 S206G, R207Y, Y208L, L209M, M226I;  
A183G, K185E, E186R, K187E, T188G, F197Y,  
M198R, D201T, P205Y, S206G, R207Y, Y208L, L209M,  
M226I;  
F197Y, M198R, D201T, P205Y, S206G, R207Y,  
20 Y208L, L209M, N223H, M226I; and  
A183G, K185E, E186R, K187E, T188G, F197Y,  
M198R, D201T, P205Y, S206G, R207Y, Y208L, L209M,  
N223H, M226I.
- 25 12. The heregulin variant of Claim 9 wherein said  
heregulin variant is a fragment.
13. The heregulin variant of Claim 12 wherein said  
fragment comprises residues corresponding to a  
30 portion of human heregulin- $\beta$ 1 extending from about  
residue 175 to about residue 230.
14. A nucleic acid molecule encoding the heregulin  
variant of Claim 1.
- 35 15. A vector comprising the nucleic acid molecule of  
Claim 14.

16. A host cell comprising the vector of Claim 15.
17. A method of producing a variant of a heregulin comprising:
- 5 (a) culturing the host cell of Claim 16 under conditions that allow expression of the heregulin variant; and
- (b) recovering the heregulin variant from the culture.
- 10 18. A method of producing a heregulin variant comprising modifying the heregulin variant of Claim 1 to produce a modified heregulin variant, wherein the modified heregulin variant retains the
- 15 ability to bind an ErbB receptor.
19. The method of Claim 18 wherein said modifying step comprises introducing a modification selected from the group consisting of an amino acid
- 20 substitution, an insertion of at least one amino acid, a deletion of at least one amino acid, and a chemical modification.
20. A composition comprising the heregulin variant of
- 25 Claim 1 and a pharmaceutically acceptable carrier.
21. A method for activating an ErbB receptor comprising contacting the heregulin variant of Claim 1 with a cell that expresses said ErbB
- 30 receptor.
22. The method of Claim 21 wherein said cell is in cell culture.
- 35 23. The method of Claim 21 wherein said cell is present in a mammal.

24. The method of Claim 23 wherein said mammal is a human.
25. The method of Claim 21 wherein said contacting enhances survival, proliferation, of differentiation of said cell.
26. The method of Claim 25 wherein said cell is selected from a glial cell, a Schwann cell, and a muscle cell.
27. A method of determining whether a sample contains an ErbB receptor that binds a heregulin comprising:
- (a) contacting the heregulin variant of Claim 1 with said sample; and
  - (b) determining whether said heregulin variant specifically binds a component of said sample.
28. The heregulin variant of Claim 1 wherein said selected residue corresponds to a residue of 645-amino acid native human heregulin- $\beta$ 1 selected from the group consisting of H178, L179, and R207 and said heregulin variant has a greater specificity for the ErbB-4 receptor, relative to the ErbB-3 receptor, than the heregulin from which said heregulin variant is derived.
29. The heregulin variant of Claim 28 wherein said heregulin is a human heregulin.
30. The variant of Claim 29 wherein said human heregulin is heregulin- $\beta$ 1.
31. The heregulin variant of Claim 30 wherein said amino acid substitution is selected from

H178E and R207P.

32. The heregulin variant of Claim 28 wherein said heregulin variant is a fragment.

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33. The heregulin variant of Claim 32 wherein said fragment comprises residues corresponding to a portion of human heregulin- $\beta$ 1 extending from about residue 175 to about residue 245.

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34. A variant of a heregulin, said variant having an amino acid sequence not found in nature and the ability to bind an ErbB receptor, wherein said variant comprises a deletion of amino acid residues corresponding to residues S228 to K231 of 645-amino acid native human heregulin- $\beta$ 1 and a substitution therefor of a methionine, wherein said residues of 645-amino acid native human heregulin- $\beta$ 1 are numbered from the N-terminus of native human heregulin- $\beta$ 1, said heregulin variant having a greater specificity for the ErbB-4 receptor, relative to the ErbB-3 receptor, than the heregulin from which said heregulin variant is derived.

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35. The heregulin variant of Claim 34 additionally comprising the amino acid substitution H178L.

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36. The heregulin variant of Claim 34 wherein said heregulin is a human heregulin.

37. The variant of Claim 36 wherein said human heregulin is heregulin- $\beta$ 1.

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38. The heregulin variant of Claim 34 wherein said heregulin variant is a fragment.

39. The heregulin variant of Claim 37 wherein said fragment comprises residues corresponding to a portion of human heregulin- $\beta 1$  extending from about residue 175 to about residue 245.